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Oral Abstract – O311

Abacavir and the altered peptide repertoire model: clinical implications

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Structural and biochemical studies showing that abacavir binds non-covalently to the floor of the peptide binding groove of HLA-B*5701 with exquisite specificity to alter the self-peptides that load on the molecule to be presented to the immune system have recently been published [1–4]. This precise mechanistic explanation of why abacavir binds to HLA-B*5701 and no other allele accounts for the 100% negative predictive value of HLA-B*5701 testing for hypersensitivity which underpins its utility as a screening test. The specificity of the interaction between abacavir, peptide and HLA-B*5701 provides strong evidence that abacavir will not cause any off-target, HLA restricted immune-mediated side effects in HLA-B*5701 negative individuals. The rapid and direct non-covalent binding of abacavir to HLA-B*5701 without the requirement for metabolism of the drug explain the clinical symptoms of hypersensitivity including dose-related escalation of symptoms and rapid offset of symptoms following drug cessation. Importantly, if abacavir were being developed today its propensity to bind HLA-B*5701, alter the peptide repertoire presented, and the functional consequences of this interaction between HLA-B*5701 and abacavir could be determined in vitro and before use in man. This provides an important pre-clinical screening strategy to identify compounds in development that bind HLA and alter peptide presentation which could then be structurally modified to abrogate this property to avert hypersensitivity while retaining on-target effects.

References

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